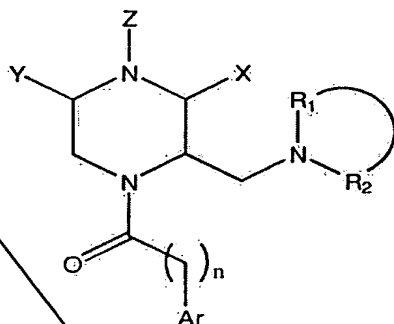


WHAT IS CLAIMED IS:

1 ✓ A pharmaceutical composition for the prevention or treatment of pruritus comprising a compound of formula I or a pharmaceutically acceptable salt thereof



(I)

5 wherein

$n = 1-3$;

R_1 and R_2 are independently $=CH_3$; $-(CH_2)_m$, where $m =$
 4-8, $-CH_2CH(OH)(CH_2)_2-$; $-CH_2CH(F)(CH_2)_2-$;

$-(CH_2)_2O(CH_2)_2-$; or $-(CH_2)_2CH=CHCH_2-$;

Ar = unsubstituted or mono-, or di-substituted phenyl

wherein said substituents are selected from the group

consisting of halogen, OCH_3 , SO_2CH_3 , CF_3 , amino, alkyl,

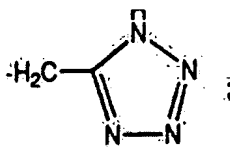
and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl;

diphenyl methyl; or 9-fluorene;

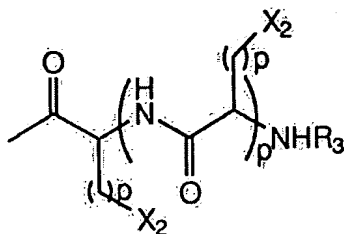
15 Z is

$-P(O)(OBn)_2$; $-P(O)(OH)_2$; $-(CH_2)_pC(O)NHOH$; $-(CH_2)_pCO_2H$; $-SO_2CH_3$; $-SO_2NH_2$;
 $CO(CH_2)_pCH(NH_2)(CO_2H)$; $-COCH(NH_2)(CH_2)_pCO_2H$; $-CO_2CH_3$; $-CONH_2$;
 $-(CH_2)_pO(CH_2)_pCO_2H$; $-(CH_2)_pO(CH_2)_pCONHOH$; $-(CH_2)_pNHSO_2CH_3$; -
 $(CH_2)_pNHC(S)NHCH(CO_2H)(CH_2)_pCO_2H$; $-(CH_2)_pSO_3H$; or

or Z is



wherein



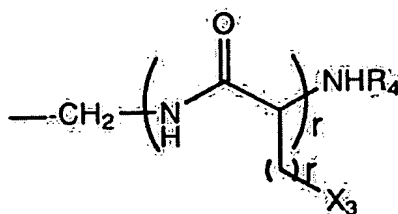
$p = 0 - 20$;

$R_3 = -H$ or $-Ac$;

$X_2 = -CO_2H$; $-NHSO_2CH_3$; $NHP(O)(OBn)_2$; $NHP(O)(OH)_2$;
 $OP(O)(OBn)_2$; or $OP(O)(OH)_2$

X and Y are independently

$-CH_2NHSO_2CH_3$, $-CH_2NHP(O)(OBn)_2$, $-CH_2NHPO(OH)_2$, $-CH_2OP(O)(OBn)_2$, $CH_2OP(O)(OH)_2$, $(CH_2)_qO(CH_2)_qCO_2H$,
 $(CH_2)_qO(CH_2)_qSO_3H$, $(CH_2)_qO(CH_2)_qCHNHOH$,
 $CH_2NHC(S)NHCH(CO_2H)(CH_2)_qCO_2H$, or



wherein

q = 1-20

r = 1-20

R₄ = -H or -Ac

- 5 X₃ = -CO₂H; -NHSO₂CH₃; -NHP(O)(OBn)₂;
 -NHP(O)(OH)₂; -OP(O)(OBn)₂; or
 -OP(O)(OH)₂

in a pharmaceutically acceptable carrier.

2. The pharmaceutical composition according to claim 1 wherein said compound is
 10 selected from the group consisting of: (4-[1-(3,4-Dichlorophenyl)acetyl-2R-(1-pyrrolidinyl)-
 methyl]piperazinyl)acetic acid; [1-(3,4-Dichlorophenyl)acetyl-4-methanesulfonyl-2R-(1-
 pyrrolidinyl)methyl]piperazine; [4-S-Aspartic acid- α -amido-1-(3,4-dichlorophenyl)acetyl-
 2R-(1-pyrrolidinyl)methyl]piperazine; Methyl-[2R-(O-2-acetic acid)hydroxymethyl-4-(3,4-
 15 dichlorophenyl)acetyl-3R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[2R-(O-
 S-aspartic acid- α -acetyl)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-3R-(1-
 pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[4-(3,4-dichlorophenyl)acetyl-2R-(N-
 methanesulfonamido)aminomethyl-3R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate;
 Methyl-{4-[3,4-dichlorophenyl]acetyl-3R-(1-pyrrolidinyl)methyl-2R-[N-(succinic acid-2S-
 20 thioureido)]aminomethyl-1-piperazinecarboxylate; Methyl-[2S-(O-2-acetic
 acid)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-
 piperazinecarboxylate; Methyl-[2S-(O-S-aspartic acid- α -acetyl)hydroxymethyl-4-(3,4-
 dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[4-(3,4-
 dichlorophenyl)acetyl-2S-(N-methanesulfonamido)aminomethyl-5R-(1-pyrrolidinyl)methyl]-
 1-piperazinecarboxylate; Methyl-{4-[3,4-dichlorophenyl]acetyl-5R-[1-pyrrolidinyl)methyl-
 25 2S-[N-(succinic acid-2S-thioureido)]aminomethyl-1-piperazinecarboxylate; Methyl-[2R-(O-
 2-acetic acid)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-
 piperazinecarboxylate; Methyl-[2R-(O-S-aspartic acid- α -acetyl)hydroxymethyl-4-(3,4-
 dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate; Methyl-[4-(3,4-
 dichlorophenyl)acetyl-2R-(N-methanesulfonamido)aminomethyl-5R-(1-pyrrolidinyl)methyl]-
 30 1-piperazinecarboxylate; and Methyl-{4-[3,4-dichlorophenyl]acetyl-5R-[1-
 pyrrolidinyl)methyl-2R-[N-(succinic acid-2S-thioureido)]aminomethyl}-1-
 piperazinecarboxylate.
3. The pharmaceutical composition according to claim 1 wherein said compound is
 selected from the group consisting of:

(R)-4-(Phenylmethyl)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine hydrochloride;

(R)-1-[(3,4-Dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine hydrochloride;

(R)-4-Methanesulfonyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(R)-4-t-Butyl-acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]- piperazine;

(R)-4-(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazineacetic acid dihydrochloride;

(R)-4-N-t-Boc-D-aspartic acid- β -benzyl ester-1 -[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine;

(R)-4-Aspartic acid-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine dihydrochloride;

(R)-4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(R)-4-(Diethoxyphosphonate)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(R)-4-Trifluoroacetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(R)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxamide hydrochloride;

(R)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxaldehyde hydrochloride;

(R)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazine-sulfonamide hydrochloride;

(R)-4-(4-Methylphenylsulfonyl)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl] - piperazine hydrochloride;

(*R,S*)-4-Methanesulfonyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride;

(*R,S*)-4-Methanesulfonyl-1-[(4-methylsulfonylphenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

5 (*R,S*)-4-Methanesulfonyl-1-[(2-nitrophenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

(*R,S*)-4-Methanesulfonyl-1-[(4-trifluoromethylphenyl)acetyl]-2-[(1-pyrrolidinyl)-30 methyl]piperazine hydrochloride;

10 (*R,S*)-4-Methanesulfonyl-1-[(3-indolylacetyl)-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride;

(*R,S*)-Methyl 4-[(4-methylsulfonylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate hydrochloride;

(*R,S*)-Methyl 4-[(4-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate hydrochloride;

15 (*R,S*)-Methyl 4-[(3-indolyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride;

(*R,S*)-Methyl 4-[(2-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride;

20 (*R,S*)-Methyl 4-[(2-methoxyphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride;

(*R,S*)-Methyl 4-[(2-aminophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate dihydrochloride;

(*R,S*)-4-Acetyl-1-[(4-methylsulfonylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-piperazine hydrochloride;

25 (*R,S*)-4-Acetyl-1-(4-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazinecarboxylate hydrochloride;

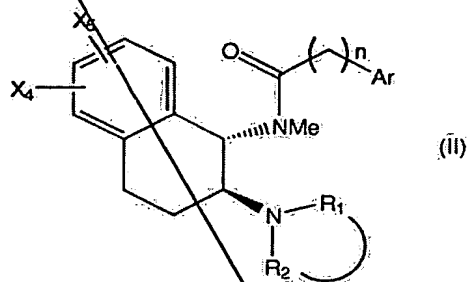
(*R,S*)-4-Acetyl-1-[(2-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazinecarboxylate hydrochloride;

(*R,S*)-4-Acetyl-1-[(3-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine-carboxylate hydrochloride;

(*R,S*)-4-Acetyl-1-[(2-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine-carboxylate hydrochloride;

5 (*R,S*)-4-Acetyl-1-[(4-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine; carboxylate hydrochloride; and

(*R,S*)-4-(Phenylmethyl)-1-[(4,5-dichloro-2-nitrophenyl)acetyl]-2-[(1-



pyrrolidinyl)methyl]piperazine dihydrochloride.

4. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 1.

5. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 2.

6. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 3.

7. A pharmaceutical composition for the prevention or treatment of pruritus comprising a compound of formula II or a pharmaceutically acceptable salt thereof wherein

$n = 1-3$;

R_1 and R_2 are independently = CH_3 ; $-(CH_2)_m$, where $m =$

4-8, $-CH_2CH(OH)(CH_2)_2$; $-CH_2CH(F)(CH_2)_2$;

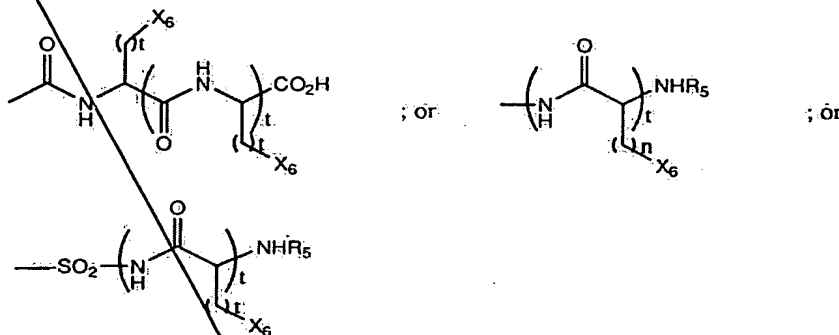
$-(CH_2)_2O(CH_2)_2$; or $-(CH_2)_2CH=CHCH_2$;

Ar = unsubstituted or mono-, or di-substituted phenyl wherein said substituents are selected from the group consisting of halogen, OCH_3 , SO_2CH_3 , CF_3 , amino, alkyl, and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl; diphenyl methyl; or 9-fluorene;

X_4 and X_5 are independently

$-\text{OP}(\text{O})(\text{OBn})_2$; $-\text{OP}(\text{O})(\text{OH})_2$; $-\text{CO}_2\text{H}$; $-\text{SO}_3\text{H}$; $-\text{O}(\text{CH}_2)_n\text{CO}_2\text{H}$;
 $-\text{NHSO}_2\text{CH}_3$; $-\text{CONH}(\text{CH}_2)_s\text{CO}_2\text{H}$; or $-\text{SO}_2\text{NH}(\text{CH}_2)_s\text{CO}_2\text{H}$; wherein
 $s = 1-5$

or X_4 and X_5 are independently



wherein

$t = 1-20$

$R_5 = -\text{H}$ or $-\text{Ac}$

$X_6 = -\text{CO}_2\text{H}$; $-\text{NHSO}_2\text{CH}_3$; $-\text{NHP}(\text{O})(\text{OBn})_2$; $-\text{NHP}(\text{O})(\text{OH})_2$; $-\text{OP}(\text{O})(\text{OBn})_2$; or
 $-\text{OP}(\text{O})(\text{OH})_2$

in a pharmaceutically acceptable carrier

8. The pharmaceutical composition according to claim 7 wherein said compound is

selected from the group consisting of: (\pm) -2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(O-2-acetic acid)-hydroxy-2-(1-pyrrolidinyl)naphthyl]acetamide; (\pm) -2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(O-2-acetic acid)-hydroxy-2-(1-pyrrolidinyl)naphthyl]acetamide; (\pm) -2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-methanesulfonamido)-amino-2-(1-pyrrolidinyl)naphthyl]acetamide; (\pm) -2-

(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-methanesulfonamido)-amino-2-(1-pyrrolidinyl)naphthyl]acetamide; (\pm) -2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-2-acetic acid)-carboxamido-2-(1-pyrrolidinyl)naphthyl]acetamide; (\pm) -2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-2-acetic acid)-sulfonamido-2-(1-pyrrolidinyl)naphthyl]acetamide; (\pm) -2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-2-acetic acid)-carboxamido-2-(1-pyrrolidinyl)naphthyl]acetamide; and (\pm) -2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-2-acetic acid)-sulfonamido-2-(1-pyrrolidinyl)naphthyl]acetamide.

9. The pharmaceutical composition according to claim 7 wherein said compound is selected from the group consisting of:

- 2-(7-[(±)-trans-1-(N-3,4-dichlorophenylacetamido-N-methylamino)-2-(1-pyrrolidinyl)-1,2,3,4-tetrahydronaphthoxy]) acetic acid;
- 2,2-Diphenyl-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-methoxy-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 5 2,2-Diphenyl-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-hydroxy-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 10 2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-amino-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(4-Methylsulfonylphenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 15 2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(t-butoxycarbonylmethyl)-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(carboxymethyl)amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 20 2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(ethoxycarbonylmethyl)-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-(N-diethylphosphoramidato-amino)-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-[1-pyrrolidinyl]-7-[N-2-(diethylphosphoryl)ethyl-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 25 2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-6-methoxy-7-(N-benzyl-N-methylaminosulfonyl)-1,2,3,4-tetrahydronaphth-1-yl]acetamide;
- 2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-(N-benzyl-N-methylaminosulfonyl)-1,2,3,4-tetrahydronaphth-1-yl]acetamide;

2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide;

2-(2-Nitro-4-trifluoromethylphenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide;

5 2,2-Diphenyl-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide; and

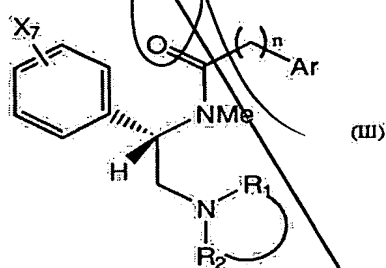
2-(4-Methylsulfonylphenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide.

10. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 7.

11. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 8.

12. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 9.

13. A pharmaceutical composition for the prevention or treatment of pruritus comprising a compound of the formula **III** or a pharmaceutically acceptable salt thereof



15 wherein

$n = 1-3$;

R_1 and R_2 are independently $= CH_3$; $-(CH_2)_m$, where $m = 4-8$,
 $-CH_2CH(OH)(CH_2)_2-$; $-CH_2CH(F)(CH_2)_2-$; $-(CH_2)_2O(CH_2)_2-$; or
 $-(CH_2)_2CH=CHCH_2-$;

20 $Ar =$ unsubstituted or mono-, or di-substituted phenyl wherein said substituted are selected from the group consisting of halogen, OCH_3 , SO_2CH_3 , CF_3 , amino, alkyl, and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl; diphenyl methyl; or 9-fluorene;

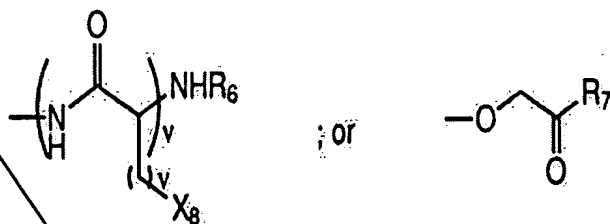
X_7 is

25 $-NHSO_2CH_3$; $-NHP(O)(OBn)_2$; $-NHP(O)(OH)_2$; $-(CH_2)_uNHSO_2CH_3$;
 $-(CH_2)_uNHC(S)NHCH(CO_2H)(CH_2)_uCO_2H$; $-CONHOH$; or $-(CH_2)_uCONHOH$;

wherein

u= 1-5; or

X₇ is



R₆ = -H or -Ac;

X₈ = -CO₂H; -NHSO₂CH₃ -NHP(O)(OBn)₂;

-NHP(O)(OH)₂; OP(O)(OBn)₂ or

-OP(O)(OH)₂;

R₇ = -NH(CH₂)_vCO₂H; -

NH(CH₂)_vCH(NH₂)(CO₂H);

-NHCH(CO₂H)(CH₂)_vNH₂; NH(CH₂)_vSO₃H₂;

-NH(CH₂)_vPO₃H₂; -

NH(CH₂)_vNHC(NH)NH₂; or

-NHCH(CO₂H)(CH₂)_vCO₂H; and

v = 1-20;

5 in a pharmaceutically acceptable carrier.

14. The pharmaceutical composition according to claim 13 wherein said compound is selected from the group consisting of:

2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-(N-2-acetic acid)carboxamido]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide; 2-(3,4-dichlorophenyl)-N-methyl-N-1-[3-(N-

10 methanesulfonamido)aminomethyl]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide; 2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-(N-succinic acid-2S-thioureido)aminomethyl]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide; and 2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-(N-2-acetic acid)sulfonamido]phenyl-2-(1-pyrrolidinyl)ethyl)acetamide.

15. The pharmaceutical composition according to claim 13 wherein said compound is
15 selected from the group consisting of:

~~2-(3,4-Dichlorophenyl)-N-methyl-N-([1S]-1-[N-(S-aspartic acid- α -amide-S-aspartic acid-amido)-3-aminophenyl]-2-[1-pyrrolidinyl]ethyl)acetamide;~~

~~2-(3,4-Dichlorophenyl)-N-methyl-N-([1S]-1-[N-(bis-methylsulfonamido)-3-aminophenyl]-2-[1-pyrrolidinyl]ethyl)acetamide;~~

5 ~~2-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

~~2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

~~2-(N-Diethyl phosphoramidate-2-aminophenyl)-N-methyl-N-[(1S)-1-(N-diethyl phosphoramidate-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

10 ~~2-(N-Bis-sulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-(N-bis-sulfonamido-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

~~2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

~~2-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

15 ~~2-(N-Butyloxycarbonyl-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

~~2-(4-Aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

~~2-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

20 ~~2-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

~~2-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(N-diethyl phosphoramidate-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide;~~

25 ~~2-(2-Nitrophenyl)-N-methyl-N-([1S]-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl)acetamide;~~

~~2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-([1S]-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl)acetamide;~~

2-(4-Methylsulfonylphenyl)-N-methyl-N-([1S]-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl)acetamide;

2-(2-Nitro-4-trifluoromethylphenyl)-N-methyl-N-([1S]-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl)acetamide;

5 2-(2-Amino-4-trifluoromethylphenyl)-N-methyl-N-([1S]-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl)acetamide;

2,2-Diphenyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

N',N'-Diphenyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl] urea;

2-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

10 2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Methoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(3-Indolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

15 2-(α,α,α -Trifluoro-p-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Nitro- α,α,α -Trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(1-[4-Chlorobenzoyl]-5-methoxy-2-methyl indole)-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

20 2-(4-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(3-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(3-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

25 2-(+)-6-Methoxy- α -methyl-2-naphthalene)-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(α,α,α -Trifluoro-3-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

- 2-(4-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(α,α,α -Trifluoro-2-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-((S)-(+)-4-Isobutyl-x-methylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 5 2-(3,4,5-Trimethoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 10 2-(N-Methylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-Amino 4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(N,N-Dimethylsulfonamido-2-amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl 2-(1-pyrrolidinyl)ethyl]acetamide;
- 15 2-(2-Amino,x,x,x-Trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-N,N-Dimethylsulfonamido-2-amino- α,α,α -trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 20 2-(N-Methylsulfonamido-2-amino- α,α,α -trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(4-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 2-(N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;
- 25 2-(N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide;

2-(2-Hydroxyphenyl)-N-methyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide; and

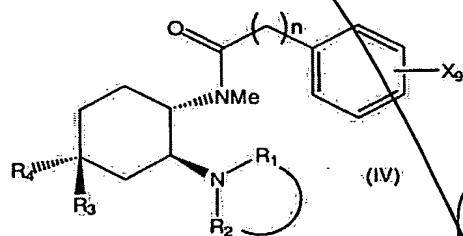
N-Methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidine-1-yl)ethyl]-3,4,5-trimethoxyphenylacetamide.

5 16. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 13.

17. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 14.

10 18. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 15

19. A pharmaceutical composition for the prevention or treatment of pruritus comprising a compound of the formula IV or a pharmaceutically acceptable salt thereof



wherein

15 $n = 1-3$;

R_1 and R_2 are independently $= CH_3$; $-(CH_2)_m$, where $m = 4-8$, $-CH_2CH(OH)(CH_2)_2-$; $-CH_2CH(F)(CH_2)_2-$; $-(CH_2)_2O(CH_2)_2-$; or $-(CH_2)_2CH=CHCH_2-$;

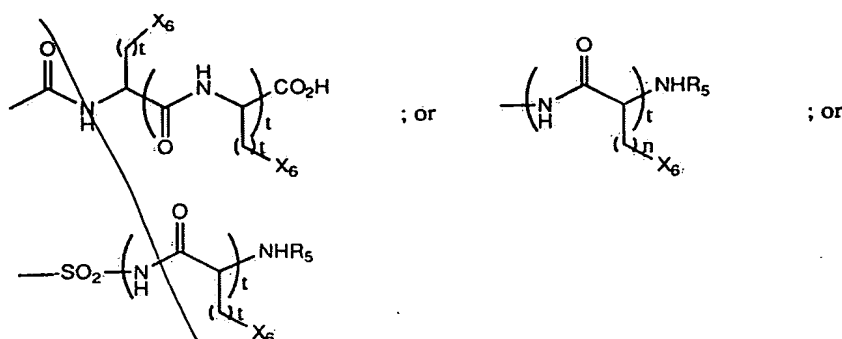
R_3 and R_4 are independently H; OCH_3 alkyl; or $c-O(CH_2)_2$

20 $X_9 = 1-4$ substituents selected from the groups consisting of

-halogen; $-CF_3$; $-OCH_3$; $-SO_2NH(CH_2)_qCO_2H$; $CONH(CH_2)_qCO_2H$; $-NH_2$; $-NHSO_2CH_3$; $-NHP(O)(OBn)_2$; $-NHP(O)(OH)_2$; $NH(CH_2)_qCO_2H$; $-SO_2CH_3$; $-OP(O)(OBn)_2$; $-OP(O)(OH)_2$; $-CO_2H$; $O(CH_2)_qCO_2H$; $-O(CH_2)_qSO_3H$;; $-O(CH_2)_qOPO_3H_2$; wherein

25 $q = 1-20$;

or X_9 is



wherein

t = 1-20;

R₅ = -H or -Ac;

X₅ = -CO₂H; -NH₂SO₂CH₃; -NHP(O)(OBn)₂;

-NHP(O)(OH)₂; -OP(O)(OBn)₂; or

-OP(O)(OH)₂

in a pharmaceutically acceptable vehicle.

20. The pharmaceutical composition according to claim 19 wherein said compound is selected from the group consisting of:

(-)-(5 α ,7 α ,8 β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-methanesulfonamido)aminophenylacetamide; (-)-(5 α ,7 α ,8 β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-2-acetic acid)sulfonamidophenylacetamide; and (-)-(5 α ,7 α ,8 β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-2-acetic acid)carboxamidophenylacetamide.

21. The pharmaceutical composition according to claim 19 wherein said compound is selected from the group consisting of:

(\pm)-*trans*-2-Nitro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide

Hydrochloride;

(\pm)-*trans*-2-Amino-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide

Hydrochloride;

(\pm)-*trans*-2-Nitro-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide

Hydrochloride;

(\pm)-*trans*-2-Amino-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide

Hydrochloride;

(\pm)-*trans*-2-Methanesulfonamido-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-

phenylacetamide Hydrochloride;

N-[2-(±)-*trans*-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamido]glycine Hydrochloride;

(±)-*trans*-4-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

5 (±)-*trans*-2-Nitro-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(±)-*trans*-2-Amino-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

10 (±)-*trans*-2-Bismethanesulfonamido-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(±)-*trans*-2-Methanesulfonamido-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

N-[2-(±)-*trans*-4-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamido]glycine Hydrochloride;

15 (±)-*trans*-3-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(±)-*trans*-5-Nitro-3-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

20 (±)-*trans*-2-Nitro-3-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(±)-*trans*-2-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(±)-*trans*-4-Nitro-2-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

25 (±)-*trans*-4-Amino-2-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride;

(±)-*trans*-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]2,2-diphenylacetamide Hydrochloride; and

30 (±)-*trans*-4-Methylsulfonyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide Hydrochloride.

22. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 19.

23. A method for the prevention or treatment of pruritus in a patient comprising administering to said patient an effective amount of a composition according to claim 20.

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